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Eptifibatide and Low-Dose Tissue Plasminogen Activator in Acute Myocardial Infarction

The Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) Trial

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OBJECTIVES This study was designed to test the hypothesis that eptifibatide and reduced-dose tissue plasminogen activator (t-PA) will enhance infarct artery patency at 60 min in patients with acute myocardial infarction (AMI).

BACKGROUND Combination fibrin and platelet lysis improves epicardial and myocardial reperfusion in AMI.

METHODS Patients were enrolled in a dose finding (Phase A, n = 344) followed by a dose confirmation (Phase B, n = 305) protocol. All patients received aspirin and weight-adjusted heparin and underwent angiography at 60 and 90 min. In Phase A, eptifibatide in a single or double bolus (30 min apart) of 180, 180/90 or 180/180 μg/kg followed by an infusion of 1.33 or 2.0 μg/kg per min was sequentially added to 25 or 50 mg of t-PA. In Phase B, patients were randomized to: 1) double-bolus eptifibatide 180/90 (30 min apart) and 1.33 μg/kg per min infusion with 50 mg t-PA (Group I); 2) 180/90 (10 min apart) and 2.0 μg/kg per min with 50 mg t-PA (Group II); or 3) full-dose, weight-adjusted t-PA (Group III).

RESULTS In Phase A, the best rate of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 was achieved using 180/90/1.33 μg/kg per min eptifibatide with 50 mg t-PA: 65% and 78% at 60 and 90 min, respectively. In Phase B, the incidence of TIMI flow grade 3 at 60 min was 42%, 56% and 40%, for Groups I through III, respectively ($p = 0.04$, Group II vs. Group III). The median corrected TIMI frame count was 38, 33 and 50, respectively ($p = 0.02$). TIMI major bleeding was reported in 8%, 11% and 6%, respectively; intracranial hemorrhage occurred in 1%, 3% and 2% of patients ($p > 0.5$ for both). The incidences of death (4%, 5% and 7%), reinfarction or revascularization at 30 days were similar among the three treatment groups.

CONCLUSIONS In comparison with standard t-PA regimen, double-bolus eptifibatide (10 min apart) with a 48-h infusion and half-dose t-PA (Group II) is associated with improved quality and speed of reperfusion. The safety profile of this therapy is similar to that of other combination regimens. (J Am Coll Cardiol 2002;39:377–86) © 2002 by the American College of Cardiology

Rapid and complete restoration of blood flow achieved with fibrinolytic therapy improves myocardial function and survival after acute myocardial infarction (AMI) (1). Nevertheless, current regimens of full-dose plasminogen activators achieve Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in 50% to 60% of patients by 90 min, and approximately 20% of patients have a combination of reocclusion or microvascular obstruction (2). In addition, fibrinolytic agents are associated with a significant risk of intracranial hemorrhage (ICH), particularly in older patients (3).

Given the key role platelets play in coronary thrombosis, two recent studies (4,5) using abciximab and reduced-dose tissue plasminogen activator (t-PA) or recombinant plasminogen activator have shown promising results. Eptifibatide, a peptide glycoprotein (GP) IIb/IIIa inhibitor with rapid onset of action and reversibility, was previously evaluated in conjunction with full-dose t-PA (6) and streptokinase (7). In the former study, a reduced dose of eptifibatide combined with full-dose t-PA produced a substantially higher rate of TIMI flow grade 3 at 90 min than t-PA alone (66% vs. 39%, $p < 0.05$). The latter study, using single-bolus eptifibatide, demonstrated a significant increase in

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[1]Deceased.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
aPTT	= activated prothrombin time
cTFC	= corrected TIMI frame count
ECG	= electrocardiogram
GP	= glycoprotein
GUSTO	= Global Utilization To Open occluded coronary arteries
ICH	= intracranial hemorrhage
LAD	= left anterior descending artery
TIMI	= Thrombolysis In Myocardial Infarction
t-PA	= tissue plasminogen activator

combined TIMI flow grade 2 + 3 at 60 min and a trend for improved TIMI flow grade 3 (44% for combination therapy vs. 31% for placebo). On the basis of accumulated pharmacokinetic data and modeling, double-bolus regimens were designed to achieve and maintain a receptor occupancy ≥80% during the critical first 90 min after reperfusion therapy (8). Thus, we performed a dose finding and confirmation study to test the angiographic efficacy of various doses of bolus and infusion of eptifibatide and reduced-dose t-PA in AMI.

METHODS

This was an angiographic, Phase II open-label trial with a sequential design during the dose finding phase and formal randomization during the confirmation phase. Between February 17, 1998, and June 13, 2000, 649 patients with AMI were enrolled at 55 centers in North America, Europe and South Africa. Patients over the age of 18 were eligible for enrollment if they presented with ischemic discomfort for >20 min within 6 h of onset and ST-segment elevation and were candidates for fibrinolytic therapy. Important exclusion criteria included the usual contraindications to fibrinolysis, previous surgical revascularization, serum creatinine >2.0 mg/dl, cardiogenic shock requiring intra-aortic balloon counterpulsation, use of another GP IIb/IIIa receptor antagonist within seven days, or known intolerance to aspirin, heparin, eptifibatide or t-PA. After screening and informed consent, patients received at least 160 mg aspirin and heparin 4,000 U (60 U/kg for weight <70 kg) bolus followed by an 800 U/h (12 U/h for weight <70 kg) infusion, to maintain an activated prothrombin time of 50 to 70 s for up to 24 h. The protocol was reviewed and approved at each institution by the appropriate ethics/investigation review board.

Study Protocol

Dose finding phase (Phase A). Patients were enrolled sequentially into eight different combination therapy regimens, as shown in Table 1. Eptifibatide was administered immediately after (within 30 min) t-PA, except in Groups 7 and 8 in which eptifibatide was given before t-PA (within 15 min). When double-bolus eptifibatide was used, it was given 30 min apart. The eptifibatide infusion was continued for 72 h. Tissue plasminogen activator was given as a 25 mg bolus (Group 1 and 2) or 15 mg bolus and 60-min infusion of 35 mg in Groups 3 to 8. Transition from dose regimen group to group was based on a prespecified review by the steering and safety committees of the safety and efficacy data of at least 30 patients enrolled in a particular group.

Basis for double bolus regimens of eptifibatide. In addition to the approved single-bolus regimen of 180 μg/kg bolus and 2.0 μg/kg per min infusion, eptifibatide was administered in a double-bolus form of 180/90 μg/kg and 180/180 μg/kg. The dosing regimens used in clinical trials of GPIIb-IIIa inhibitors have targeted a level of platelet aggregation inhibition of at least 80% of baseline. An eptifibatide plasma concentration of 1,600 ng/ml results in the desired level of receptor occupancy and inhibition of platelet aggregation. The single-bolus regimen of 180 μg/kg achieves the minimum 1,600 ng/ml plasma concentration. However, it is frequently accompanied by a transient decrease in drug concentration below 1,600 ng/ml at 30 to 60 min following the initial bolus (9–11).

Dose confirmation phase (Phase B). The best regimen from the dose finding phase was selected for Phase B (180/90 μg/kg, 30 min apart plus a 1.33 μg/kg per min infusion, Group I). An additional eptifibatide dosing strategy (180/90 μg/kg, 10 min apart plus a 2.0 μg/kg per min infusion, Group II) was selected to ascertain whether the interval between boluses has an effect on angiographic patency (Table 1). This phase was open-label and was initiated with a standard lytic arm (front-loaded, weight-adjusted 90-min infusion of ≤100 mg of t-PA) serving as the control group (Group III). In Group II, the infusion of eptifibatide could be reduced to 1.33 μg/kg per min if minor bleeding occurred, according to investigator judgment. The eptifibatide infusion was continued for a maximum of 48 h (18 to 24 h if revascularization was performed).

Angiography. Angiography was performed at 60 and 90 min following administration of the t-PA bolus, unless the investigator considered the need for immediate angioplasty to be critical. An independent angiographic laboratory adjudicated all films with respect to TIMI flow (12) and corrected TIMI frame count (cTFC) (13). A value of 100 was assigned to patients with TIMI flow grade 0 to 1. The reviewers were blind to patient assignment.

Primary and secondary end points. The primary efficacy end point was the incidence of TIMI flow grade 3 at 60 ± 15 min after the administration of t-PA bolus (60 min window). The key secondary end point consisted of the incidence of TIMI flow grade 3 at 90 ± 15 min (90 min window). The primary safety end point was the incidence of TIMI major bleeding during the initial hospitalization (4).

Patients were monitored for 30 days after enrollment for the occurrence of death (cardiac or noncardiac), reinfarction, stroke (hemorrhagic or nonhemorrhagic), percutaneous or surgical revascularization, development of heart

Table 1. Baseline Characteristics (Includes Patients Who Received Study Drug)

Group	1	2	3	4	5	6	7	8	I	II	III
Sequence	t-PA Followed by Eptifibatide						Eptifibatide Followed by t-PA		t-PA Followed by Eptifibatide		
t-PA	25 mg IV Bolus			15 mg IV Bolus + 35 mg IV Infusion Over 60 min					15 mg IV Bolus + 35 mg IV Infusion Over 60 min		15 mg IV Bolus + 0.75 mg/kg Over 30 min + 0.5 mg/kg Over 60 min
Eptifibatide											
Bolus #1 μg/kg	180	180	180	180	180	180	180	180	180	180	
Bolus #2 μg/kg		90		90	180	180		90	90	90	
Infusion μg/kg per min	1.33	1.33	1.33	1.33	1.33	2.0	2.0	2.0	1.33	2.0	
No. of patients	35	37	31	52	54	48	33	48	99	100	100
Age (yr)	63 (54,69)	62 (56,69)	61 (52,73)	60 (50,70)	60 (51,69)	60 (52,70)	59 (51,68)	59 (53,67)	60 (50,68)	59 (49,71)	59 (50,68)
Gender—male	23 (65)	29 (70)	26 (83)	34 (65)	39 (72)	36 (75)	26 (81)	42 (87)	73 (74)	78 (78)	78 (78)
HTN	17 (48)	16 (43)	13 (41)	21 (40)	17 (31)	20 (41)	14 (43)	20 (41)	46 (47)	36 (36)	41 (41)
Diabetes	9 (25)	8 (21)	5 (16)	9 (17)	9 (16)	11 (22)	6 (18)	4 (8)	16 (16)	21 (21)	13 (13)
Prior MI	4 (11)	4 (10)	4 (12)	7 (13)	7 (13)	3 (6)	4 (12)	4 (8)	16 (16)	18 (18)	16 (16)
Pain to Rx, h	3.1	3.3	2.7	2.8	2.9	3.1	3.2	3.3	2.9	3.0	3.0
Lytic to eptifibatide, min	16 (6,24)	11 (3,17)	11 (3,16)	9 (3,15)	10 (3,15)	5 (2,7)	−6 (−10,−2)	−8 (−10,−5)	3 (1,4)	3 (0,4)	
Lytic to angio, min	60	60	60	60	59	60	59	58	60	57	58
MI Location											
Anterior	11 (31)	12 (32)	5 (16)	15 (29)	24 (44)	22 (46)	12 (38)	23 (48)	37 (37)	36 (36)	33 (33)
Inferior	24 (69)	25 (68)	25 (81)	34 (65)	25 (46)	21 (44)	20 (63)	23 (48)	58 (59)	56 (56)	56 (56)
Other	7 (21)	11 (30)	10 (33)	19 (37)	16 (30)	14 (29)	8 (25)	6 (12)	30 (30)	36 (36)	26 (26)

Data presented as number (%) or medians (with 25th to 75th percentile), as appropriate.
HTN = hypertension; IV = intravenous; MI = myocardial infarction; t-PA = tissue plasminogen activator.

failure or pulmonary edema, recurrent ischemia (>5 min) or cardiogenic shock.

Reinfarction in the first 24 h was diagnosed if ST elevation reoccurred or there was re-elevation of CK-MB (33% for a previous decrease from peak of ≥25% or 100% for a preceding decrease of ≥50%). Reinfarction after 24 h was diagnosed based on CK-MB re-elevation to above 3 times normal (2 times normal after day 7) or new significant Q waves. Stroke was diagnosed on the basis of an imaging study and an expert neurologist opinion. Percutaneous or surgical revascularization was considered an end point if performed for TIMI flow grade <3 flow. All patients had an electrocardiogram (ECG) performed at baseline and 3 h after administration of the t-PA bolus. An independent ECG laboratory reviewed all tracings and determined the degree of ST elevation resolution, according to Schroeder's criteria (14).

Statistics

Phase A. A minimum of 30 patients per group allowed for at least 96% probability (one-sided) of detecting a TIMI flow grade 3 of at least 60% based on a historical control rate of 39% for full-dose t-PA at 60 min and at least 70% with a historical control of 54% at 90 min. Enrolling 45 patients in each group ensured at least a probability of 70% of detecting a rate of major bleeding of at least 7% based on a historical control rate of 5% (6).

Phase B. On the basis of these assumptions, enrolling 100 evaluable patients in each group afforded a 80% power (two-sided, 0.05 alpha) to detect an absolute 20% difference in the 60-min rate of TIMI flow grade 3 between each experimental group and the control patients.

Data are presented, when appropriate, as number and/or percentage of patients. Continuous data are presented as means with standard deviation or medians with 25th to 75th percentile ranges. Student *t* and Wilcoxon rank-sum tests were performed, as indicated, without correction for multiple-group comparison.

RESULTS

The baseline characteristics of the patients are shown in Table 1. One-fourth of the patients were women and nearly one-fifth had treated diabetes mellitus. The majority of patients were current or recent ex-smokers, and a third of the patients suffered an anterior infarction.

Angiographic outcome. The adjudicated incidence of TIMI flow grade 3 in each stage and group at 60 and 90 min is shown in Table 2. Of the 649 patients randomized, 641 (98.6%) received the assigned study drug regimen and an angiogram and were thus considered the evaluable cohort for the primary end point. In Phase A, patients receiving half-dose t-PA over 1 h and double-bolus eptifibatide of 180 and 90 μg/kg, followed by a 1.33 μg/kg per min infusion had the highest rate of TIMI flow grade 3 (Group 4) of 65% (95% confidence interval 52% to 78%) at 60 min and 78% (65% to 91%) at 90 min. The cTFC analysis confirmed this observation; median frame counts decreased to 26 for this dose group and the cumulative frame count demonstrated a left shift with the double-bolus regimen, indicating more rapid blood flow. No incremental benefit was seen as the dose of the second bolus was increased from 90 to 180 μg/kg. Reperfusion regimens consisting of quarter-dose t-PA were noted to be less effective.

Phase A provided a unique opportunity to evaluate the effects of sequence of administration of eptifibatide and t-PA on infarct artery patency. There was a statistically significant increase in TIMI flow grade 3 at 60 and 90 min in the groups that received t-PA followed by eptifibatide as compared with the opposite sequence (Groups 3 and 4 vs. Groups 7 and 8, $p = 0.046$), confirmed by a significantly lower cTFC ($p = 0.04$, Fig. 1).

In Phase B, using the predefined window of 60 ± 15 min, patients assigned to Group II had a significantly higher incidence of TIMI flow grade 3 compared with Group III (56% [45% to 67%] vs. 40% [29% to 51%], respectively, $p = 0.04$). However, this benefit was not apparent when the interval between boluses was increased from 10 to 30 min and the infusion was lowered (Group I vs. Group III). At 90 min, combination therapy (Group II) demonstrated a trend toward a persistent advantage over the control patients (Group III) (62% [51% to 73%] vs. 54% [42% to 66%], $p = 0.11$, respectively). The incidence of TIMI flow grade 3 at 60 and 90 min in the full-dose t-PA control group is consistent with previous studies.

The incidence of TIMI flow grade 3 did not change significantly if angiograms obtained outside of the prespecified time window were considered, using the best available data. The rates of TIMI flow grade 3 in Groups I, II and III at 60 and 90 min were 42%, 54% and 40% ($p = 0.04$ for Group II vs. Group III) and 46%, 59% and 47% ($p = 0.08$ for Group II vs. Group III), respectively.

The cTFCs in the infarct-related artery in the three groups of Phase B are shown in Table 2 and Figure 2. Patients in Group II had a significantly lower median cTFC than those in Group III (33 vs. 50, $p = 0.02$, respectively) at 60 min. There was an upward and leftward shift indicating faster flow in Group II compared with Group III ($p = 0.02$). No significant difference existed between Groups I and III.

ST- segment resolution. The degree of complete (≥70%) ST-segment elevation 3 h after the t-PA bolus is shown in Table 3. In Phase A, the highest rate of resolution was observed again in Group 4, corresponding to the highest rate of TIMI flow grade 3. There were no significant differences among the three groups in Phase B. There was substantially more frequent complete resolution of ST-segment elevation in patients with inferior MI (78%, 84% and 80%) than in those with anterior MI (44%, 44% and 42%), for Groups I through III, respectively.

Clinical outcome. The incidence of death, reinfarction or need for revascularization is listed in Table 3. There were no

Table 2. Angiographic Results (Includes Patients Who Received Study Drug)

Group	1	2	3	4	5	6	7	8	I	II	III
Sequence	t-PA Followed by Eptifibatide						Eptifibatide Followed by t-PA		t-PA Followed by Eptifibatide		
t-PA	25 mg IV Bolus			15 mg IV Bolus + 35 mg IV Infusion Over 60 min					15 mg IV Bolus + 35 mg IV Infusion Over 60 min		15 mg IV Bolus + 0.75 mg/kg Over 30 min + 0.5 mg/kg Over 60 min
Eptifibatide											
Bolus #1 μg/kg	180	180	180	180	180	180	180	180	180	180	
Bolus #2 μg/kg		90		90	180	180		90	90	90	
Infusion μg/kg/min	1.33	1.33	1.33	1.33	1.33	2.0	2.0	2.0	1.33	2.0	
No. of Patients	35	37	31	52	54	48	33	48	99	100	100
60 min window	25	31	27	48	44	38	30	40	84	75	81
TIMI 3	12 (48)	14 (45)	16 (59)	31 (65)	27 (61)	17 (45)	14 (47)	20 (50)	35 (42)	42 (56)	32 (40)
TIMI 2/3	21 (84)	24 (77)	23 (85)	45 (94)	37 (84)	34 (89)	25 (83)	36 (90)	63 (75)	60 (80)	55 (68)
cTFC	33 (23,64)	49 (28,100)	31 (24,37)	26 (20,38)	35 (23,57)	36 (22,65)	41 (28,100)	37 (24,48)	38 (24,100)	33 (18,91)	50 (29,100)
60 min end point*	33	37	29	51	53	46	33	48	96	96	96
TIMI 3	17 (52)	17 (46)	17 (59)	33 (65)	33 (62)	18 (39)	16 (48)	22 (46)	40 (42)	52 (54)	38 (40)
TIMI 2/3	28 (85)	29 (78)	24 (83)	48 (94)	46 (87)	40 (87)	28 (85)	39 (81)	73 (76)	73 (76)	66 (69)
c-TFC	32 (22,64)	37 (25,100)	31 (24,57)	27 (20,39)	35 (22,54)	37 (25,66)	39 (26,71)	41 (24,60)	38 (23,100)	34 (19/100)	46 (26,100)
90 min window	28	32	26	37	39	40	20	29	72	79	69
TIMI 3	14 (50)	12 (38)	15 (58)	29 (78)	29 (74)	21 (53)	15 (75)	17 (59)	38 (53)	49 (62)	37 (54)
TIMI 2/3	23 (82)	28 (88)	22 (85)	35 (95)	37 (95)	35 (88)	20 (100)	27 (93)	62 (86)	65 (82)	54 (78)
cTFC	28 (24,62)	36 (25,61)	34 (21,60)	23 (14,38)	31 (23,38)	35 (22,53)	28 (19,37)	32 (24,44)	32 (22,55)	31 (14,92)	36 (22,100)
90 min end point	33	37	29	51	53	46	33	48	96	96	96
TIMI 3	18 (55)	14 (38)	18 (62)	37 (73)	36 (68)	24 (52)	18 (55)	25 (52)	44 (46)	57 (59)	45 (47)
TIMI 2/3	28 (85)	30 (81)	25 (86)	48 (94)	46 (87)	40 (87)	29 (88)	40 (93)	65 (68)	74 (77)	68 (71)
cTFC	28 (24,61)	37 (25,100)	32 (20,45)	25 (17,39)	31 (23,49)	34 (22,59)	36 (22,52)	32 (24,44)	36 (23,100)	31 (19,98)	41 (24,100)

*End point 60′ = Missing data estimated by selecting first available data as follows: TIMI-initial followed by TIMI 90′ followed by TIMI-final. End point 90′ = Missing data estimated by selecting first available data as follows: TIMI-final followed by TIMI 60′ followed by TIMI-initial. Data presented as number (%) or medians with 25th to 75th percentile, as appropriate.

cTFC = corrected TIMI frame count; TIMI = Thrombolysis In Myocardial Infarction. Other abbreviations as in Table 1.

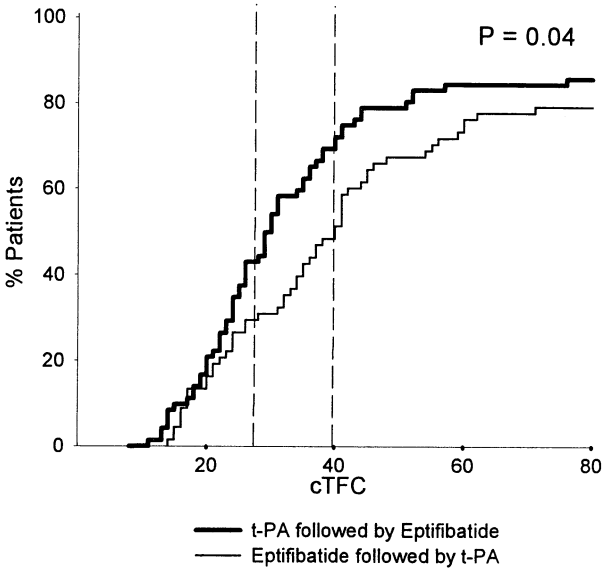


Figure 1. Corrected Thrombolysis In Myocardial Infarction (TIMI) frame count for various sequences of administration of the components of the combination regimen. The vertical lines at 27 and 40 frames indicate the accepted upper limit of corrected TIMI frame count (cTFC) for TIMI flow grade 3 and the breakpoint between TIMI flow grades 3 and 2, respectively. t-PA = tissue plasminogen activator.

significant differences among the three groups in Phase B. Clinically indicated revascularization, defined as all coronary artery bypass grafting (CABG) and percutaneous coronary intervention for recurrent ischemia or TIMI flow grade <3, was performed in 80 of 305 patients (26%) and was the lowest in Group II (26%, 23% and 31% for Groups I through III, respectively). There were 346 patients who underwent percutaneous revascularization, 177 (52%) in Phase A and 169 (55%) in Phase B. Of these, 24 (14%) in Phase A and 33 (20%) in Phase B (13, 8 and 12 for Groups I through III, respectively) had angioplasty before the 90-min angiogram.

Safety end points. Intracranial hemorrhage was reported in 11 (1.7%, 95% confidence intervals 0.8% to 3.0%) patients, whereas the overall rate of TIMI major hemorrhage using combination therapy was 10.5% (Table 3). All-cause mortality was 4.8% (31/641 patients who received study drug).

Phase A. Intracranial hemorrhage occurred in 5 (1.5% [0.5% to 3.4%]) patients without apparent differences among the regimens tested. The incidence of TIMI major bleeding (excluding CABG) was 15% (n = 48), the majority of which was related to bleeding at the access site (12.8%, n = 44). The incidence of TIMI major bleeding (excluding CABG) in the groups receiving single-bolus eptifibatide (Groups 1, 3 and 7: 180 μg/kg), double-bolus (Groups 2, 4 and 8: 180/90 μg/kg) and higher double-bolus (Groups 5 and 6: 180/180 μg/kg) was 9.3%, 17.1% and 19.4%, respectively, p = 0.14. Lower dose t-PA (Groups 1 and 2) was not associated with less major bleeding. Moderate thrombocytopenia (<100,000 platelets/mm^3) occurred in 13 patients (3.8%). Two patients (0.6%) experienced severe thrombocytopenia (<50,000 platelets/mm^3). Transfusions were administered in 16% (n = 55), with the lowest rate in Group 4 (13.2%).

Phase B. The incidence of TIMI major bleeding was 8%, 11% and 6%, in Groups I through III, respectively. A total of six patients experienced ICH (one, three and two patients, respectively, 2% [0.7%–4.4%], p = NS). Transfusion of blood products occurred in 16%, 13% and 11%, but only in seven patients excluding CABG (2.3%), and thrombocytopenia was not observed in any patient.

DISCUSSION

This study is the first systematic evaluation of eptifibatide administered with reduced-dose t-PA for the treatment of AMI and is one of four angiographic trials of a GPIIb IIIa inhibitor combined with reduced-dose fibrin lysis com-

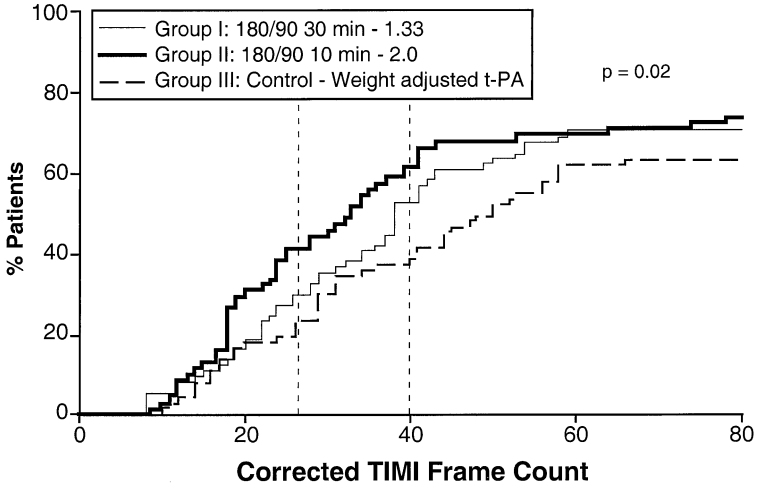


Figure 2. Corrected Thrombolysis In Myocardial Infarction (TIMI) frame count for the dose confirmation phase. The vertical lines at 27 and 40 frames indicate the accepted upper limit of cTFC for TIMI flow grade 3 and the breakpoint between TIMI flow grades 3 and 2, respectively. t-PA = tissue plasminogen activator.

Table 3. Safety and Clinical Events Through 30 Days (All Randomized Patients)

Group	1	2	3	4	5	6	7	8	I	II	III
Sequence	t-PA Followed by Eptifibatide						Eptifibatide Followed by t-PA		t-PA Followed by Eptifibatide		
t-PA	25 mg IV Bolus		15 mg IV Bolus + 35 mg IV Infusion Over 60 min						15 mg IV Bolus + 35 mg IV Infusion Over 60 min		15 mg IV Bolus + 0.75 mg/kg Over 30 min + 0.5 mg/kg Over 60 min
Eptifibatide											
Bolus #1 μg/kg	180	180	180	180	180	180	180	180	180	180	
Bolus #2 μg/kg		90		90	180	180		90	90	90	
Infusion μg/kg per min	1.33	1.	1.33	1.33	1.33	2.0	2.0	2.0	1.33	2.0	
No. of patients	35	37	31	52	54	48	33	48	102	102	101
All-cause death	4 (12)	1 (3)	2 (6)	1 (2)	0	3 (6)	2 (6)	2 (4)	4 (4)	5 (5)	7 (7)
Cardiac death	2	1	2	1	0	1	1	1	3	3	4
Re-MI	0	0	1 (3)	4 (8)	1 (2)	2 (4)	3 (9)	1 (2)	8 (8)	2 (2)	3 (3)
ST analysis											
No. of patients	29	33	27	48	42	35	25	37	86	83	85
>70% resolution	22 (76)	25 (76)	18 (67)	38 (79)	27 (64)	19 (54)	17 (68)	26 (70)	56 (65)	57 (69)	56 (66)
PCI (clinically indicated)	9 (27)	12 (36)	8 (24)	13 (26)	12 (24)	12 (24)	10 (30)	11 (23)	26 (26)	23 (23)	31 (31)
Major bleeding											
Non-CABG	1 (3)	4 (11)	2 (6)	4 (8)	6 (11)	8 (17)	4 (13)	8 (17)	8 (8)	11 (11)	6 (6)
Spontaneous	1 (3)	0	0	0	1 (2)	3 (6)	3 (9)	2 (4)	2 (2)	1 (1)	1 (1)
ICH	1	0	0	0	1	1	1	1	1	3	2
Thrombocytopenia (<50,000/mm^3)	0	0	0	1	0	0	0	1	0	0	0

Data presented as number (%) or medians (with 25th to 75th percentile), as appropriate.

CABG = coronary artery bypass grafting; ICH = intracerebral hemorrhage; IV = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention; t-PA = tissue plasminogen activator.

pleted to date (4,5,15). Two large trials assessing the effect of combination therapy on mortality (16,17) have been completed, creating a collective experience in excess of 20,000 patients.

Comparison with similar studies. This trial demonstrated that eptifibatide-mediated inhibition of platelet aggregation in conjunction with half-dose t-PA enhances the rate of TIMI flow grade 3, and even more importantly, speeds the process of reperfusion, such that most of the effect is already observed by 60 min. Phase A showed that a double-bolus strategy of eptifibatide coupled to reduced-dose (50 mg) t-PA yielded TIMI flow grade 3 rates at 60 and 90 min that exceed previously reported reperfusion rates with t-PA alone. Moreover, the TIMI flow grade 3 observed in this study compared favorably with other combination regimens and with data from large studies of primary angioplasty (18). In Phase B, the combination regimen demonstrated a 16% absolute advantage over full-dose t-PA at 60 min. However, this advantage was only seen when the double-bolus regimen was given at the shorter 10-min interval and in conjunction with the higher infusion rate. This finding highlights the fact that an aggressive strategy of platelet GPIIb/IIIa receptor inhibition and fibrinolysis enhances the speed and rate of reperfusion. This 16% advantage in TIMI flow grade 3 is similar to the 18% difference observed at 60 min in the TIMI 14 trial (4), and superior to the 7% difference noted in the Strategies for Patency Enhancement in the Emergency Department (SPEED) study (5). The reduction in the difference between the combination and control patients at 90 min is likely due to the widespread use of PCI (>15%) before the 90-min angiographic end point.

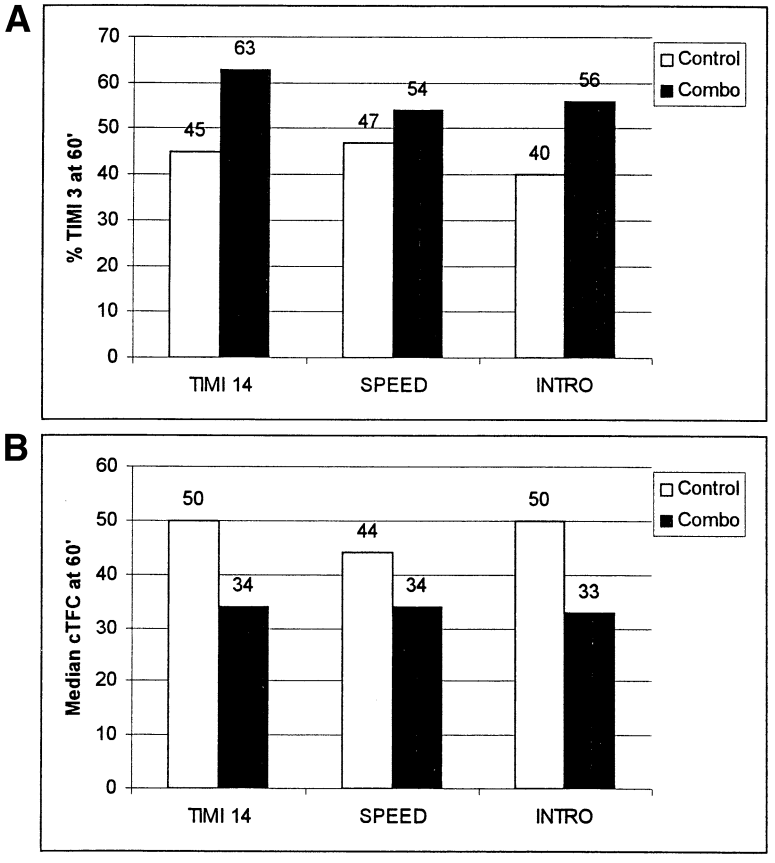
Furthermore, when the continuous variable of cTFC is analyzed (Fig. 3), there is remarkable consistency between this study and the two previously reported studies of abciximab (19). The rather large differences in arterial patency for the 180/90/1.33 eptifibatide regimen between the two phases of the study highlight the limitation of very small groups of patients studied for an angiographic end point, although the results in Phase B fall within the 95% confidence interval for Phase A. Noteworthy is the fact that Group 4 had a lower incidence of left anterior descending coronary artery infarct (30%), which was an independent predictor of failed lysis in TIMI 14.

Myocardial reperfusion, represented by complete resolution of ST-segment elevation, was frequent in this study. In phase B, there were no significant differences among the three groups, in whom two-thirds of the patients demonstrated excellent reperfusion. However, the second ECG was performed after PCI in more than half of the cases. Therefore, direct comparison of our ECG data with other combination therapy studies cannot be made (20).

Higher rates of bleeding complications were reported in Phase A than in similar studies, particularly among recipients of the 180/180 μg/kg double-bolus of eptifibatide. The dose of t-PA did not appear to impact on hemorrhagic risk. In Phase B, the incidence of major bleeding was similar to that observed in the other trials and in line with AMI trials with mandatory angiography and high rates of immediate revascularization. As a comparison, the incidence of TIMI major bleeding was 7% in the combination abciximab and t-PA in TIMI 14 (4). In SPEED (5), severe hemorrhage occurred in 9.8% of the 112 patients treated with the combination regimen. When full-dose t-PA was used either alone or in conjunction with escalating modest doses of eptifibatide (36 to 180 μg/kg bolus and 0.2 to 0.75 μg/kg per min infusion), the rate of severe hemorrhage was only 2% for the combination group and 5% for t-PA alone, suggesting that more aggressive platelet inhibition plays an important role in this complication (6). Nevertheless, approximately 75% of the bleeding episodes occurred at the catheterization access site, suggesting that meticulous attention to sheath care and removal and judicious antithrombin therapy may alleviate this problem. Overall, non-ICH bleeding complications had little impact on the clinical outcome. In general, the rate of major hemorrhage is expected to be higher in angiographic studies because of the mandatory instrumentation, and indeed there is an 8–10% incidence of major hemorrhage in the primary angioplasty studies, in which lytic therapy is not administered (21). Typically, the definition of major bleeding in those studies was also less stringent than the TIMI criteria.

Study limitations. A number of issues regarding combination therapy for AMI have not yet been addressed. First, it is not clear whether differences in the fibrinolytic agents influence outcome. Second, the incidence of major clinical end points was low, and thus we cannot be certain that the angiographic superiority demonstrated by the combination regimens will translate into survival benefit or a reduction in recurrent ischemic events. Particular attention should be paid to the incidence of ICH, because an important goal of the combination therapy is to minimize this dreaded complication. The large Global Utilization of Strategies To Open occluded coronary arteries (GUSTO) V-AMI study, comparing standard fibrinolysis with the SPEED regimen of combination therapy, did not show an increase in ICH in the combination therapy arm, except for patients older than 75 years. Third, we did not adjust statistically for multiple group comparisons, which could have exaggerated the actual significance of differences between groups. Finally, approximately 20% of the patients in the confirmation phase did not undergo angiography per protocol. Nevertheless, using the data closest to the prespecified window and including 95% of the patients did not alter the results substantially.

Conclusions. Double-bolus (within a 10-min interval) and high-dose infusion of eptifibatide combined with half-dose t-PA is superior to standard dose t-PA alone in achieving reperfusion of the infarct-related artery 60 min after initiation of therapy. The 16% absolute difference in TIMI flow rate 3 is comparable to the results of similar studies and was achieved without a significant increase in major bleeding events, although a higher nominal rate of ICH was observed in the patients with the highest rate of reperfusion. More



Panel A: 95% confidence intervals for rates of TIMI 3 flow:

TIMI 14: 63% (50%-76%) vs. 45% (35%-55%)
SPEED: 54% (44%-64%) vs. 47% (37%-57%)
INTRO AMI: Group II 56% (45%-67%) vs. Group III 40% (29%-51%)

Panel B: 25%-75% interquartile range for median cTFC:

TIMI 14: 34 (27-43) vs. 50 (30-100)
SPEED: 34 (25, 100) vs. 44 (24, 100)
INTRO AMI: Group II 33 (18-91) vs. Group III 50 (29-100)

Figure 3. **(A)** Incidence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 at 60 min in trials of combination therapy, adapted from references 3 and 4. **(B)** Median corrected TIMI frame count (cTFC) in trials of combination therapy, adapted from references 3 and 4. INTRO AMI = Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction trial; SPEED = Strategies for Patency Enhancement in the Emergency Department.

than 75% of the episodes of major bleeding were associated with the catheterization access site and did not affect clinical outcome. The clinical utility of this strategy hinges on the tradeoff between safety and efficacy and awaits confirmation in larger clinical trials designed to detect differences in mortality and other key outcomes of AMI.

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For a complete list of Investigators and Coordinators, as well as Steering and Safety Committee members, of the INTRO AMI Study, please see the February 6, 2002 issue of *JACC* at www.cardiosource.com

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REFERENCES

1. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–22.

2. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis: A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699–705.
3. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation 2000;101:2239–46.
4. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis In Myocardial Infarction (TIMI) 14 trial. Circulation 1999;99:2720–32.
5. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000;101:2788–94.
6. Ohman EM, Kleiman NS, Gacioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators. Circulation 1997;95:846–54.
7. Ronner E, van Kesteren HA, Zijnen P, et al. Safety and efficacy of eptifibatide vs placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction: a phase II dose escalation, randomized, double-blind study. Eur Heart J 2000;21:1530–6.
8. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037–44.
9. Kosoglou TBB, Jennings L. Eptifibatide pharmacokinetic-pharmacodynamic relationship in coronary angioplasty patients: results of the PRIDE study. Eur Heart J 1997;19 Suppl:52.
10. Tcheng JE, Thel MC, Jennings L. Platelet glycoprotein IIb/IIIa receptor blockade with high-dose Integrilin in coronary intervention: results of the PRIDE study. Eur Heart J 1997;18:P3615.
11. Gilchrist IC, O'Shea JC, Kosoglou T, et al. Pharmacodynamics and pharmacokinetics of higher-dose, double-bolus eptifibatide in percutaneous coronary intervention. Circulation 2001;104:406–11.
12. Chesebro J, Knatterud G, Roberts R, et al. Thrombolysis In Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142–54.
13. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
14. Schroder R, Dissmann R, Bruggemann T, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994;24:384–91.
15. Giugliano RP, Roe MT, Zeymer U, et al. Restoration of epicardial and myocardial perfusion in acute ST-elevation myocardial infarction with combination eptifibatide+reduced-dose tenecteplase: dose-finding results from the INTEGRITI trial (abstr). Circulation 2001;104.
16. The ASSENT 3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. Lancet 2001;358:605–13.
17. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001;357:1905–14.
18. The GUSTO IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–8.
19. Moliterno DJ, Antman EM, Ohman E, et al. Concordance between core labs in trial results using TIMI flow grades and frame counts (abstr). Circulation 2000;102:II-590.
20. de Lemos JA, Antman EM, Gibson CM, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: Observations from the TIMI 14 trial. Circulation 2000;101:239–43.
21. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–8.

APPENDIX A

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APPENDIX B

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